

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084479 A3(51) International Patent Classification⁷: C12Q 1/70,
C12N 7/00, A61K 31/395

(21) International Application Number: PCT/US03/09274

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/368,706 29 March 2002 (29.03.2002) US(71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
20 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LARGE SCALE METHODS OF PRODUCING ADENOVIRUS AND ADENOVIRUS SEED STOCKS

(57) Abstract: A process for large scale virus production is disclosed, especially large scale adenovirus production. The methods described are preferably adapted to suspension culture of mammalian host cells in a large scale bioreactor where gas sparging becomes essential to provide adequate aeration through the duration of the culture. This methodology includes an elevated concentration of a compound which protects host cells from the shearing effects of gas sparging and agitation as well as utilizing virus seed stocks which have been generated free of cell lysis reagents. The invention also relates to methods of producing these virus seed stocks, which are scaleable and the resultant unclarified virus seed stocks which are concentrated to reduce storage volume for infection of large scale culture and which are free of cell lysis components, such as the detergent Triton X-100 or Polysorbate 80.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/09274

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/70; C12N 7/00; A61K 31/395

US CL : 435/5, 235.1; 424/233.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/5, 235.1; 424/233.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,194,191 B1 (ZHANG et al) 27 February 2001 (27.02.2001), abstract, column 2, lines 58-61, column 4, lines 24-28, column 11, lines 1-11, column 12, line 49, column 13, lines 18-20, column 19, lines 6-64, and column 20, lines 7-14.	1-46

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

13 August 2003 (13.08.2003)

Date of mailing of the international search report

30 SEP 2003

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

PCT/US03/09274

Continuation of B. FIELDS SEARCHED Item 3:

APS, CAS ONLINE, MEDLINE, BIOSIS, EMBASE, CAPLUS, SCISEARCH

search terms: zhou, xie, altaras, aunins, detergent, freeze-thaw, cell culture, adenovirus, bioreactor, shear, pluronic, harvest, seed stock